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RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. §1.116	Attorney Docket No.	PALO-004
	Confirmation No.	8822
	First Named Inventor	YUN, ANTHONY JOONKYOO
	Application Number	10/748,976
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	Group Art Unit	3762
Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Kahelin, Michael William
	Title: "TREATMENT OF FEMALE FERTILITY CONDITIONS THROUGH MODULATION OF THE AUTONOMIC NERVOUS SYSTEM"	

Sir:

This communication is responsive to the Final Office Action dated December 26, 2007, for which a three-month period for response was given making this response due by March 26, 2007. Accordingly, this response is timely filed.

LISTING OF THE CLAIMS

In the Claims:

1. (Previously Presented) A method of treating a female subject for a fertility condition, said method comprising:

providing a female subject known to suffer from said fertility condition; and

modulating at least a portion of the autonomic nervous system of said female subject to increase the sympathetic activity/parasympathetic activity ratio of said subject in a manner effective to treat said female subject for said fertility condition, wherein said method further comprises determining said sympathetic activity/parasympathetic activity ratio at least prior to said modulation and performing said modulation of said at least one portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio.

2. (Original) The method of Claim 1, wherein said modulation is performed during at least one predetermined phase of said subject's menstrual cycle.

3. (Original) The method of Claim 2, wherein said predetermined phase is the luteal phase.

4. (Original) The method of Claim 1, wherein said increase of the sympathetic activity/parasympathetic activity ratio comprises increasing sympathetic activity.

5. (Original) The method of Claim 1, wherein said increase of the sympathetic activity/parasympathetic activity ratio comprises decreasing parasympathetic activity.

6. (Original) The method of Claim 1, wherein said increase of the sympathetic activity/parasympathetic activity ratio comprises increasing sympathetic activity and decreasing parasympathetic activity.

7. (Original) The method of Claim 1, wherein said modulation is localized.

8. (Original) The method of Claim 7, wherein said modulation is localized to at least one pelvic nerve.

9. (Original) The method of Claim 1, wherein said modulation is accomplished by at least applying electrical energy to said at least one portion of said autonomic nervous system.

10. (Original) The method of Claim 9, wherein said application of electrical energy comprises electrically increasing activity in at least one portion of said autonomic nervous system.

11. (Original) The method of Claim 9, wherein said application of electrical energy comprises electrically inhibiting activity in at least one portion of said autonomic nervous system.

12. (Withdrawn) The method of Claim 1, wherein said modulation is accomplished by at least administering an effective amount of at least one pharmacological agent to said subject.

13. (Withdrawn) The method of Claim 12, wherein said at least one pharmacological agent is chosen from: beta agonists, alpha agonists, prednisone, steroids, indirect agents that include norepinephrine, epinephrine, norepinephrine, acetylcholine, sodium, calcium, angiotensin I, angiotensin II, angiotensin converting enzyme I, angiotensin converting enzyme II, aldosterone, potassium channel blockers,

magnesium channel blockers, cocaine, amphetamines, ephedrine, terbutaline, dopamine, doputamine, antidiuretic hormone, oxytocin, THC cannabinoids, and combinations thereof.

14. (Withdrawn) The method of Claim 12, wherein said method comprises combining said at least one pharmacological agent with seminal fluid to provide an at least one pharmacological agent containing seminal fluid mixture and administering said mixture to said subject.

15 – 16. (Canceled)

17. (Original) The method of Claim 1, wherein said method further comprises determining said sympathetic activity/parasympathetic activity ratio at least during said modulation.

18. (Original) The method of Claim 1, wherein said method further comprises determining said sympathetic activity/parasympathetic activity ratio at least following said modulation.

19. (Original) The method of Claim 1, further comprising determining the ratio of Th-1 activity/Th-2 activity.

20. (Original) The method of Claim 1, wherein said fertility condition is infertility.

21. (Withdrawn) The method of Claim 1, wherein said infertility condition is subfertility.

22. (Withdrawn) The method of Claim 1, wherein said fertility condition is early pregnancy loss.

23. (Withdrawn) The method of Claim 1, wherein said fertility condition is spontaneous abortion.

24. (Withdrawn) The method of Claim 1, wherein said fertility condition is an implantation failure.

25. (Withdrawn) The method of Claim 1, wherein said fertility condition is amenorrhea.

26. (Withdrawn) The method of Claim 1, wherein said fertility condition is luteal insufficiency.

27. (Withdrawn) The method of Claim 1, wherein said fertility condition is dysmenorrhea.

28. (Withdrawn) The method of Claim 1, wherein said fertility condition is chemical pregnancy loss.

29. (Withdrawn) The method of Claim 1, wherein said fertility condition is stillbirth.

30. (Withdrawn) The method of Claim 1, wherein said fertility condition is habitual abortion.

31. (Withdrawn) The method of Claim 1, wherein said fertility condition is endometriosis.

32. (Withdrawn) A kit comprising:

(a) at least one of: an electric energy supplying device and at least one pharmacological agent; and

(b) instructions of using said at least one of said electric energy supplying device and said at least one pharmacological agent in a method according to Claim 1.

33. (Withdrawn) The kit of Claim 32, wherein said kit comprises at least one pharmacological agent.

34. (Withdrawn) The kit of Claim 33, wherein said kit comprises a plurality of pharmacological agents.

35. (Withdrawn) The kit of Claim 34, wherein at least two of said plurality differ in at least one aspect.

36. (Withdrawn) The kit of Claim 35, wherein said at least one aspect is dosage.

37. (Withdrawn) The kit of Claim 35, wherein said at least one aspect is the type of pharmacological agents.

38. (Withdrawn) The kit of Claim 32, wherein said kit includes an electric energy supplying device.

REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1-11 and 17-20, the only claims pending and under examination in this application.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 4, 7, 9, 10, 17, 18 and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai (US Publication No. 2005/0065574) in view of Verrier et al. (5,437,285).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. See Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (citing KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007))); and see Omegaflex, Inc. v. Parker-Hannifin Corp., 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (citing KSR Int'l Co. at 1741)); and see Dystar Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (citing In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

The rejected claims are directed to a method of treating a female subject known to suffer from a fertility condition. The method includes modulating at least a portion of the autonomic nervous system of the female subject to increase the sympathetic

activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition.

The method further includes determining the ratio of sympathetic activity to parasympathetic activity prior to the modulation and performing the modulation of a portion of the autonomic nervous system based on the determined ratio of sympathetic activity to parasympathetic activity.

In making the rejection, the Office alleges that Rezai discloses modulating a portion of the autonomic nervous system of a female subject known to suffer from a fertility condition, because Rezai includes the conditions of 'infertility' and 'painful menses' in the list of "hypothalamic-related conditions".

Rezai assertedly discloses affecting a "hypothalamic-related condition" by electrically or chemically stimulating the hypothalamus (see Abstract). However, Rezai discloses a list of over 55 conditions allegedly related to the hypothalamus. These conditions include an extremely diverse range of conditions including infertility, baldness, narcolepsy, lethargy, dwarfism, and facial blushing (page 3, Table II). Importantly, Rezai does not provide any further teaching or suggestion as to how the method is to be applied specifically to each condition.

Furthermore, the Office acknowledges that Rezai does not disclose determining a ratio of sympathetic activity to parasympathetic activity. With respect to this deficiency, the Office asserts that Rezai discloses a closed-loop system to control the autonomic stimulation for treating a fertility condition (Office Action, p. 6). The Office therefore relies upon Verrier, et al., which allegedly teaches that sympathetic/parasympathetic balance is one such “pattern of neuronal activity” that is used as a feedback mechanism of autonomic influence for stimulators.

The Applicants respectfully disagree with this assertion. Verrier et al. disclose a method directed to individuals with potentially fatal heart conditions. In the "Abstract", Verrier et al. state that the method is "for predicting susceptibility to sudden cardiac death simultaneously assessing cardiac electrical stability and autonomic influence" (Abstract, emphasis added). In the "Summary of the Invention", Verrier et al. state that the method disclosed is for diagnosing "cardiac vulnerability to ventricular fibrillation" (and col. 6, lines 4-5). In the "Detailed Description of the Preferred Embodiment", Verrier et al. state the method is for "individuals at risk for sudden cardiac death" (col. 9, lines 50-51, emphasis added). The ratio in Verrier is a ratio of the low frequency component and the high frequency component of heart rate variability, which Verrier et al. disclose that it is "indicative of sympathetic activity or vagal withdrawal" (col. 7, lines 28-29).

For these reasons, it is very clear that Verrier et al. only disclose determining a ratio of the low frequency component and the high frequency component of heart rate variability of an individual with a potentially fatal heart condition.

Accordingly, the Applicants maintain that the references cited fail to teach or suggest all the elements of the claimed invention. Rezai fails to provide any teaching or suggestion as to modulating at least a portion of the autonomic nervous system of a female subject known to suffer from a fertility condition in a manner effective to treat the fertility condition, and Rezai further does not teach or suggest determining a ratio of sympathetic activity to parasympathetic activity. The addition of Verrier does not make up for this deficiency, because Verrier simply discloses a ratio of the low frequency component and the high frequency component of heart rate variability of an individual with a potentially fatal heart condition.

The Applicants note that the Examiner cites Schuler (US 2006/0224189) (Office Action, p. 7) for support for a feedback mechanism of autonomic influence. Schuler discloses a “method to record, store and broadcast specific brain waveforms to

modulate body organ functioning" (see title). There is no disclosure in this reference of measuring a sympathetic activity/parasympathetic activity ratio, or measuring a ratio of any kind. It is not clear to the Applicants how this reference provides support for the Examiner's argument.

Furthermore, the Applicants note that the cited portion of the specification of Rezai is as follows: "In particular, the sensors may detect the *rate and pattern of the neuronal activity* to determine the stimulation signal to be provided to the stimulator." (paragraph 0048, lines 20-22; p. 10; emphasis added). As disclosed in Rezai, the closed-loop feedback mechanism includes "detecting a physiological activity of the body associated with the hypothalamic-related condition to generate a sensor signal" (paragraph 0047, lines 9-11) which is further disclosed as "[e]xamples of electrical activity detected by sensors located within or proximal to the target site include sensors that measure neuronal electrical activity, such as the electrical activity characteristic of the signaling stages of neurons (i.e. synaptic potentials, trigger actions, action potentials, and neurotransmitter release) at the target site and by afferent and efferent pathways and sources that project to and from or communicate with the target site." (paragraph 0048, lines 8-15)

In other words, the method in Rezai includes a simple measurement of neuronal activity. The "sensor signal" for the closed-loop feedback mechanism in Rezai is, therefore, a measurement such as synaptic potential. There is no disclosure in Rezai of determining a ratio of neuronal activity, which would require measuring sympathetic activity, measuring parasympathetic activity, and then comparing the two measured activities to determine a ratio.

Rezai is therefore silent as to determining a ratio of any kind. The ratio in Verrier is specifically limited to patients with heart conditions, and there is no indication or suggestion in the references that determining a ratio of the low frequency component

and the high frequency component of heart rate variability as in heart patients would have any relevance to treating a female for a fertility condition.

The Examiner has therefore failed to provide a valid apparent reason why one of skill in the art would modify Rezai with the teaching of Verrier.

In *KSR*, the Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR*, 127 S. Ct. at 1741. Put another way, the Court stated that it is important to "determine whether there was an apparent reason to combine the known elements in the way a patent claims." *Id.* "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

The Examiner has asserted that Rezai teaches a closed-loop system to control the autonomic stimulation for treating a fertility condition, as discussed above, and that sympathetic/parasympathetic balance is one such "pattern of neuronal activity" that is used as a feedback mechanism of autonomic influence for stimulators.(Office Action, p. 7) . However, as argued above, the "sensor signal" for the closed-loop feedback mechanism in Rezai is simply measuring neuronal activity. There is no disclosure of determining a ratio of any kind. The Examiner has not provided any valid apparent reason why one of ordinary skill in the art would have combined a method of determining a ratio with a closed-loop feedback system where the "sensor signal" is a simple measurement of neuronal activity.

Furthermore, the Examiner has not provided any valid reason why one of skill in the art would combine a ratio determined to assess risk in heart patients, as in Verrier, with the methods of affecting hypothalamic-related conditions, as in Rezai.

In view of the above, the Applicants contend that a *prima facie* case of obviousness has not been established because the combination of Rezai and Verrier fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in a manner effective to treat a fertility condition, further comprising determining said sympathetic activity/parasympathetic activity ratio at least prior to said modulation and performing said modulation of said at least one portion of the autonomic nervous system based on the ratio. Furthermore, the Examiner has not pointed to any valid apparent reason why one of ordinary skill in the art would have combined the methods of Rezai with the ratio in Verrier. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 4, 7, 9, 10, 17, 18 and 20 be withdrawn.

Claims 2 and 3 have been rejected under 35 U.S.C. § 102(e) as anticipated by Rezai, or in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Rezai in view of Bothe Loncar et al. (US Publication No. 2002/0188336).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see Akzo N.V. v. United States Int'l Trade Comm'n 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), cert denied, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art

reference must disclose every feature of the claimed invention, either explicitly or inherently. Glaxo v. Novopharm, Ltd. 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

Claims 2 and 3 depend from Claim 1. As set forth above, elements of the rejected claims are directed to a method of treating a female subject known to suffer from a fertility condition. The method includes determining a sympathetic activity/parasympathetic activity ratio and modulating at least a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio so as to treat the female subject for the fertility condition.

As described above, Rezai is deficient in that it does not disclose determining a ratio of sympathetic activity to parasympathetic activity, much less modulating at least a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio. Accordingly, the Applicants contend that Rezai does not anticipate the Applicants' invention because Rezai fails to teach every element of the rejected claims. Therefore, the Applicants respectfully request that the rejection of Claims 2 and 3 under 35 U.S.C. § 102(e) be withdrawn.

Similarly, Claims 2 and 3 are not obvious over Rezai in view of Bothe Loncar. As discussed above, Rezai does not disclose determining a ratio of sympathetic activity to parasympathetic activity, much less modulating at least a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio. Therefore, Rezai does not teach or suggest all the claim limitations. As Bothe Loncar is cited solely for its alleged disclosure of modulating the autonomic nervous system during the luteal phase of the menstrual cycle, it fails to remedy the deficiencies of Rezai.

Therefore, a *prima facie* case of obviousness has not been established because the combination of Rezai and Bothe Loncar fails to teach or suggest all the claimed limitations, namely modulating a portion of the autonomic nervous system based on the

determined sympathetic activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition. The Applicants' therefore respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 2 and 3 over Rezai in view of Bothe Loncar be withdrawn.

Claims 5, 6 and 11 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai in view of Whitehurst et al. (USPN 6,832,114).

Claims 5, 6 and 11 depend from Claim 1. As set forth above, Claim 1 is directed to a method of modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio so as to treat the female subject for a fertility condition.

As described above, Rezai discloses affecting a "hypothalamic-related condition" by electrically or chemically stimulating the hypothalamus (see Abstract), and discloses a list of over 55 conditions allegedly related to the hypothalamus (page 9, Table II). However, Rezai does not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating the ANS of the subject based on the determined sympathetic activity/parasympathetic activity ratio.

The addition of Whitehurst et al. does not cure the deficiency of Rezai. Whitehurst et al. disclose modulating a patient's pancreatic endocrine secretion by electrical stimulation to treat diabetes. However, Whitehurst et al. do not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating at least a portion of the autonomic nervous system of the subject to increase the sympathetic activity/parasympathetic activity ratio of the subject.

Since neither Rezai nor Whitehurst et al. disclose this claim element, both references, either alone or combined, do not teach or suggest all the claim limitations of Claims 5, 6 and 11.

In view of the above, the Applicants contend that a *prima facie* case of obviousness has not been established because the combination of Rezai with Whitehurst fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in manner effective to treat a female subject for a fertility condition. Consequently, the Applicants respectfully request that the the 35 U.S.C. § 103(a) rejection of Claims 5, 6, and 11 be withdrawn.

Claim 8 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai in view of Mann et al. (US Publication No. 2002/0055761).

Claim 8 depends from Claim 1. As set forth above, Rezai fails to teach or suggest modulating a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition. As Mann is cited solely for its alleged disclosure of stimulating a pelvic nerve (i.e., to treat incontinence, urgency, frequency, or pelvic pain), it fails to remedy the deficiencies of Rezai. Mann does not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating the ANS of the subject based on the determined sympathetic activity/parasympathetic activity ratio.

Since neither Rezai nor Mann et al. disclose this claim element, both references, either alone or combined, do not teach or suggest all the claim limitations of Claim 8.

Therefore, a *prima facie* case of obviousness has not been established because the combination of Rezai with Mann fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in manner

effective to treat a female subject for a fertility condition. The Applicants therefore respectfully request that the 35 U.S.C. § 103(a) rejection of Claim 8 be withdrawn.

Claim 19 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai in view of Khan et al. (US Publication No. 2002/0064501).

Claim 19 depends from Claim 1. As set forth above, elements of the rejected claims include a method of modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio so as to treat the female subject for a fertility condition. As described above, Rezai fails to teach or suggest modulating a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition.

The addition of Khan does not remedy the deficiency of Rezai. Khan discloses using an immunoregulator to treat an immune-mediated disorder, including "chronic inflammatory disease, such as diabetes type I or II, rheumatic disease, Sjogrens syndrome, multiple sclerosis, transplantation-related immune responses such as graft-versus-host-disease, post-transfusion thrombocytopenia, chronic transplant rejection, pre-eclampsia, atherosclerosis, asthma, allergy and chronic auto-immune disease, and acute inflammatory disease" (paragraph [0028]). However, Khan does not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating the ANS of the subject based on the determined sympathetic activity/parasympathetic activity ratio.

Therefore, Khan does not remedy the deficiencies of Rezai. Consequently, a *prima facie* case of obviousness has not been established because the combination of Rezai and Khan fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in manner effective to treat a female

subject for a fertility condition. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claim 19 be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 833-7770.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-004.

Respectfully submitted,
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